Differential Pathophysiology of Bacterial Translocation After Thermal Injury and Sepsis

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Bacterial translocation (BT) occurs transiently after thermal injury and may result from an ischemic intestinal insult. To evaluate continued intestinal ischemia in the ongoing BT associated with sepsis after injury, rats were randomized to (1) 30% burn injury with *Pseudomonas* wound infection (BI), (2) BI + fluid resuscitation (BI + Fluid), (3) BI after allopurinol pretreatment to inhibit xanthine oxidase (BI + Allo), or (4) BI after azapropazone pretreatment to inhibit neutrophil degranulation (BI + Aza). On postburn days (PBD) 1, 4, and 7, animals were studied for evidence of BT and intestinal lipid peroxidation. BI + Fluid, BI + Allo, and BI + Aza significantly ($p < 0.05$) reduced rates of BT and ileal lipid peroxidation acutely after thermal injury (PBD 1) compared to BI. All four groups had equally high rates of BT associated with the onset of sepsis (PBDs 4 and 7), without evidence of further intestinal lipid peroxidation. These data indicate that the chronic gut barrier failure associated with sepsis after injury occurs independently of continued intestinal ischemia.

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INCREASING EVIDENCE SUGGESTS that failure of the gastrointestinal tract to function as an effective barrier against the absorption of intraluminal bacteria and endotoxin may participate in both the acute and chronic responses to systemic injury. Bacterial translocation in animal model[1-3] and increased intestinal permeability to lactulose in humans[4,5] have been used as experimental markers of such gut barrier dysfunction. These markers increase dramatically after acute thermal injury and diminish with recovery.[2]

Gut barrier dysfunction after acute injury may result from an ischemic insult to the intestinal mucosa. Thermal injury in animal models is accompanied by an acute decrease in splanchnic blood flow occurring within hours after injury, with return to baseline levels by 24 hours after burn.[6,7] Bacterial translocation in animal models after thermal injury may be diminished significantly by treatment with mesenteric arterial infusion of vasodilators[8] or by pretreatment with angiotensin-converting enzyme or xanthine oxidase inhibitors.[7,9] It is thus postulated that hypovolemia and splanchnic vasoconstriction after cutaneous thermal injury lead to relative intestinal ischemia, with gut barrier damage produced by activation of tissue enzymes and neutrophil degranulation.

Following uncomplicated injury, gut barrier failure is a transient event, with restoration of normal function occurring within several days.[1,10] However conversion to a chronic injury state by the superimposition of infection after thermal injury leads to prolonged and more pronounced gut barrier dysfunction. In humans increased intestinal permeability to lactulose is significantly prolonged in infected burned patients as opposed to those whose clinical courses are uncomplicated by infection.[4] In rats translocating enteric organisms, present in the mesenteric lymph nodes on postburn day 1, are cleared by the fourth postburn day after uncomplicated injury, but persist through the seventh postburn day after thermal injury and infection.[10] During burn wound sepsis, translocating organisms also may progress beyond the mesenteric lymphatics to the abdominal viscera and ultimately into the bloodstream.

Previously we demonstrated that splanchnic blood flow, as determined by ^{51}Cr-labeled microspheres, is maintained at baseline levels during burn wound sepsis in rats,[11] leading us to question the role of continued intestinal ischemia in the etiology of the prolonged gut barrier failure seen

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with sepsis. While the total blood flow to the intestine appeared unchanged during burn wound sepsis, this methodology does not eliminate the possibility of intramural shunting of blood flow within the intestine resulting in mucosal ischemic injury. The purpose of the present study was thus to further evaluate whether chronic intestinal ischemia participates in the etiology of prolonged gut barrier dysfunction during sepsis after injury. To accomplish this objective, we sought to prevent intestinal ischemic injury in a model of thermal injury and subsequent burn wound sepsis through maintenance of adequate intravascular volume *via* aggressive fluid resuscitation, and inhibition of xanthine oxidase activation and neutrophil degranulation by allopurinol or azapropazone pretreatment, respectively.

Methods

Study Design

Male Wistar rats (weighing 310 ± 25 g) were randomized to (1) 30% scald burn injury with wound inoculation with 1×10^8 colony-forming units of *Pseudomonas aeruginosa* (BI); (2) burn injury and infection as above followed by fluid resuscitation with lactated Ringer's solution (0.5 mL/percentage burn/day) by intraperitoneal injection (BI + Fluid); (3) 3-day pretreatment with the xanthine oxidase inhibitor allopurinol (50 mg/kg/day; Zyloprim®, Burroughs-Welcome, Research Triangle Park, NC) by gavage followed by burn injury and infection as above (BI + Allo); or (4) 5-day pretreatment with the anti-inflammatory agent azapropazone (100 mg/kg/day; Du Pont Pharmaceuticals, Wilmington, DE) by gavage followed by burn injury and infection as above (BI + Aza). Fluid, allopurinol, and azapropazone treatments were continued after burn through the conclusion of the study period.

Body weight was recorded daily and on postburn days 1, 4, and 7 animals were killed by anesthetic overdose (n = 12 animals/group/time point) and cultures obtained of the mesenteric lymph nodes, abdominal viscera, blood and cecal contents for evidence of bacterial translocation. Peritoneal swab cultures also were obtained from the B + I + Fluid group, which had received intraperitoneal injections after burn. Caval blood samples were obtained from the B + I and B + I + Fluid groups for hematocrit determinations, and the small bowels, livers, and spleens from these groups were excised for gravimetric determinations of total mass and tissue water content. Segments of terminal ileum were obtained from all animals for assay of tissue byproducts of lipid peroxidation.

Burn and Infection Model

A 30% dorsal scald burn was produced by immersion in 95 C water for 10 seconds using a plastic template after induction of adequate general anesthesia by intraperitoneal pentobarbital, as described by Walker and Mason.[12] After burn injury, wounds were inoculated immediately with 1×10^8 *Pseudomonas aeruginosa* strain PSA 59-1244, as described by Yurt.[13] This model previously was shown to result in onset of sepsis by postburn day 4, as evidenced by the clinical signs of anorexia, conjunctival hemorrhage, piloerection, and hypothermia.[10,11,14,15] A prolonged counter-regulatory hormone response occurs,[14] and 100% mortality results within 14 days after burn.[15]

Determination of Bacterial Translocation

After anesthetic overdose, the ventral skin was cleansed with 70% isopropyl alcohol and the abdominal cavity opened. One hundred-milligram specimens of the mesenteric lymph nodes, liver, spleen, and 0.5 mL caval blood were collected using sterile techniques. Specimens were then placed in 5-mL sterile brain–heart infusion (BHI) broth and homogenized with sterile teflon-coated tissue grinding rods (Cat. No. 08-414-14D, Fisher Scientific, Pittsburgh, PA), using a modification of the technique of Berg.[16] Two hundred-microliter aliquots of each tissue homogenate were then plated on each of sheep blood and MacConkey's agar culture plates. One half-milliliter specimens of the cecal contents were similarly obtained, placed in 10-mL BHI broth, homogenized, and serially diluted in sterile saline. Aliquots of each dilution also were plated as above. All cultures were incubated at 37 C and examined for growth at 24 and 48 hours, with organisms identified by standard bacteriologic techniques. Growth of any colony-forming units of enteric bacteria on either medium was considered a positive culture.

Determination of Intestinal Content of Lipid Peroxidation Byproducts (Malondialdehyde)

One hundred-milligram segments of terminal ileum were obtained and immediately frozen in liquid nitrogen and stored at −70 C until analysis. Samples subsequently were homogenized in buffer and assayed colorimetrically for malondialdehyde (MDA) content using the thiobarbituric acid reaction as described by Ohkawa et al.[17] Briefly, 10% weight/volume ileal homogenate was mixed with sodium dodecyl sulfate and aqueous thiobarbituric acid, while pH was maintained at 3.5 with acetate buffer. Specimens were placed in a boiling water bath for 1 hour and the resultant red pigment extracted with *n*-butanol-pyridine and estimated by the spectrophotometric absorbance at 532 nm against a tetramethoxypropane standard. Malondialdehyde content was then expressed as nmol/g tissue.

Statistical Analysis

Data is reported as the mean ± standard error of the mean (SEM) where appropriate. Comparisons of the in-

cidence of positive cultures were made using chi square analysis. Comparisons of weight data and quantitative culture results were made with one-way analysis of variance (ANOVA) with Newman-Keuls multiple range testing.

Results

Figure 1 depicts changes in body weight during the study period. As previously reported,[10,11,14] the combination of burn injury and infection results in marked cachexia, as demonstrated by the 27% cumulative weight loss seen in the BI group by postburn day 7. Neither treatment with allopurinol nor azapropazone significantly prevented the body wasting associated with this model of burn wound sepsis. However, despite food intake similar to that of the other groups, animals receiving fluid resuscitation of 15 mL/day (0.5 mL/percent burn/day) had an attenuated weight loss ($p < 0.05$ *versus* all groups on postburn days 4 and 7). This occurred in association with maintenance of normal hematocrit values, as opposed to BI animals, which demonstrated significant hemoconcentration (Fig. 2).

Burn wound sepsis is accompanied by intestinal atrophy with a significant decrement of small bowel mass by postburn day 7.[10,11] Intraperitoneal administration of fluids in this model, however, resulted in increased small bowel mass on postburn day 7 compared to the unresuscitated groups, even though a similar initial loss of intestinal mass was observed in all groups (Fig. 3). Both hepatic and splenic mass also were significantly elevated in the BI + Fluid group compared to BI on postburn day 7, (liver: 6.84 ± 0.33 *versus* 5.65 ± 0.31; spleen 0.75 ± 0.05 *versus*

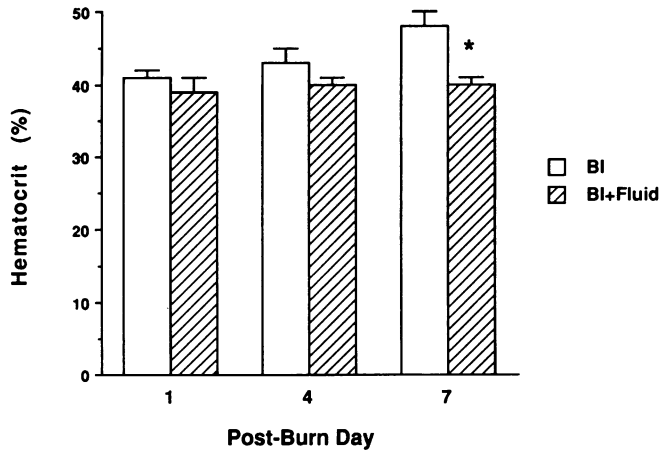

FIG. 2. Hematocrit values (mean ± SEM) during the 7-day study period. Significant hemoconcentration was evident in the unresuscitated BI group on postburn day 7 (*$p < 0.05$).

0.49 ± 0.03; $p < 0.01$ in each case). The increased organ weights in the resuscitated group appear to represent the accumulation of edema fluid within the tissues, as evidenced by a significantly increased small bowel water content (Fig. 4). Small bowel mass, but not hepatic or splenic mass, also was noted to increase in azapropazone-treated animals and may represent some local action of this drug.

The incidence of bacterial translocation to the mesenteric lymph nodes (MLN), abdominal viscera, and blood in all groups is shown in Table 1. The administration of intraperitoneal fluid resuscitation, or treatment with either allopurinol or azapropazone, significantly re-

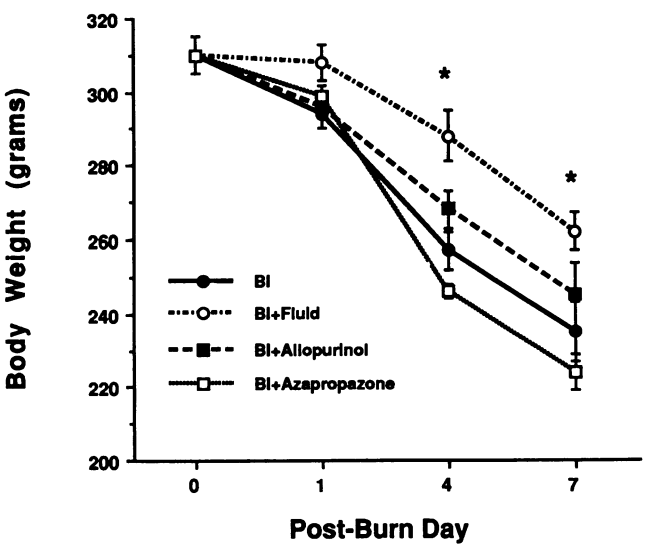

FIG. 1. Body weight change (mean ± SEM) during the 7-day study period. The BI + fluid group suffered significantly less cachexia and weight loss than all other groups (*$p < 0.05$).

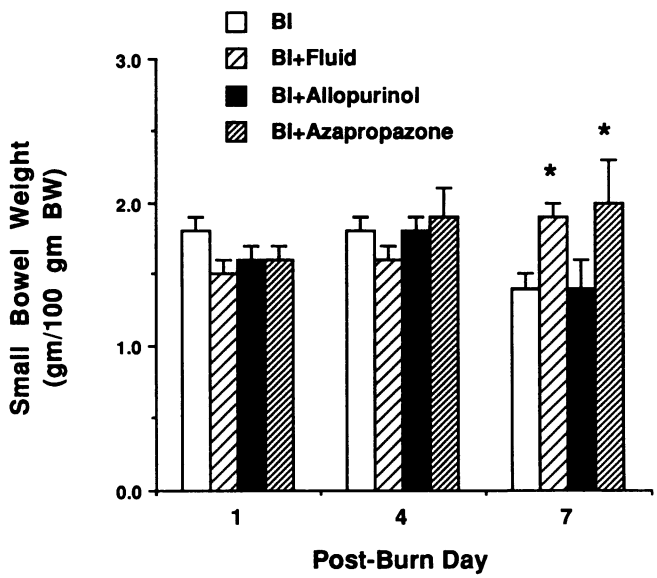

FIG. 3. Small bowel weight normalized for body weight during the 7-day study period. Significant increases in small bowel mass (mean ± SEM) were noted in the BI + fluid and BI + azapropazone groups on postburn day 7 (*$p < 0.05$).

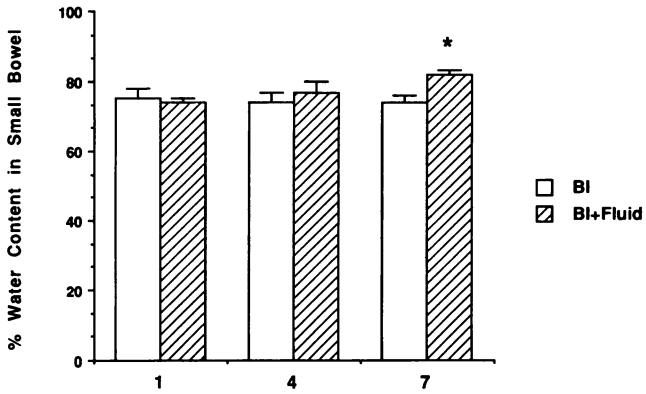

FIG. 4. Small bowel water content during the 7-day study period. Significant bowel edema, evidenced by an increase small bowel water content (mean ± SEM) was evident in the BI + fluid group by postburn day 7 (*$p < 0.05$).

duced the incidence of bacterial translocation to the MLN on postburn day 1. The abdominal viscera and blood remained sterile at this time in all groups, as in our previous report of translocation in this model.[10] However none of these regimens significantly impacted on the subsequent rates of translocation to the MLN, liver, spleen, or blood after the onset of sepsis, (postburn days 4 and 7). In all groups the predominant translocating organism was *Escherichia coli*, with the occasional appearance of other gram-negative species such as *Proteus mirabilis* and *Klebsiella pneumoniae*.

The results of quantitative cultures of the MLN, cecal flora, and burn wounds from each group are shown in Table 2. Both allopurinol and azapropazone treatment were associated with a significantly ($p < 0.05$) reduced number of enteric organisms per gram MLN compared

TABLE 1. *Bacterial Translocation of Enteric Organisms After Thermal Injury and Infection in Each Treatment Group*

Group	MLN	Liver	Spleen	Blood
Day 1				
BI	10/12*	0/12	0/12	0/12
BI + fluid	3/12	0/12	0/12	0/12
BI + allo	2/12	0/12	0/12	0/12
BI + aza	3/12	0/12	0/12	0/12
Day 4				
BI	12/12	11/12	11/12	0/12
BI + fluid	10/12	10/12	10/12	0/12
BI + allo	12/12	12/12	12/12	0/12
BI + aza	10/12	10/12	10/12	0/12
Day 7				
BI	12/12	11/12	10/12	5/12
BI + fluid	12/12	10/12	11/12	3/12
BI + allo	12/12	12/12	8/12	5/12
BI + aza	12/12	12/12	12/12	4/12

MLN, mesenteric lymph nodes; BI, burn injury and infection.
Data = positive cultures/n; translocating organisms included *E. coli, P. mirabilis,* and *K. pneumoniae.*
* $p < 0.05$ *vs.* all groups by chi square/Yates analysis.

TABLE 2. *Results of Quantitative Cultures of the Mesenteric Lymph Nodes, Cecal Contents, and Burn Wound Biopsies in Each Treatment Group*

Group	MLN	Cecal Contents†	Burn Wound‡
Day 1			
BI	206 ± 16	$6.4 \pm 0.8 \times 10^8$	$7.1 \pm 1.0 \times 10^6$
BI + fluid	250 ± 35	$3.1 \pm 2.2 \times 10^8$	$8.0 \pm 2.0 \times 10^6$
BI + allo	123 ± 13*	$2.3 \pm 1.5 \times 10^{6*}$	$1.0 \pm 0.5 \times 10^6$
BI + aza	91 ± 27*	$9.1 \pm 4.6 \times 10^{7*}$	$3.8 \pm 1.3 \times 10^6$
Day 4			
BI	1466 ± 155	$9.4 \pm 1.7 \times 10^8$	$5.9 \pm 0.5 \times 10^9$
BI + fluid	807 ± 216	$2.1 \pm 0.7 \times 10^8$	$5.9 \pm 1.3 \times 10^9$
BI + allo	1285 ± 197	$1.7 \pm 1.5 \times 10^{7*}$	$4.3 \pm 0.7 \times 10^9$
BI + aza	714 ± 297	$5.4 \pm 1.5 \times 10^8$	$5.6 \pm 2.1 \times 10^9$
Day 7			
BI	916 ± 289	$1.3 \pm 0.2 \times 10^9$	$7.1 \pm 0.3 \times 10^9$
BI + fluid	1444 ± 602	$1.7 \pm 1.0 \times 10^{8*}$	$6.6 \pm 0.6 \times 10^9$
BI + allo	1390 ± 242	$7.2 \pm 5.3 \times 10^{6*}$	$3.2 \pm 0.7 \times 10^9$
BI + aza	875 ± 260	$2.2 \pm 0.5 \times 10^{8*}$	$6.3 \pm 1.2 \times 10^9$

MLN, mesenteric lymph nodes; BI, burn injury and infection.
Data = mean ± SEM colony-forming units/g.
* $p < 0.05$ *vs.* BI by ANOVA/Newman-Keuls.
† Numbers of facultative gram-negative bacteria are shown.
‡ Pseudomonas aeruginosa was the sole organism cultured from the burn wounds of all groups at these time points.

to the BI and BI + Fluid groups on postburn day 1. No significant differences in this parameter were noted on either of the other study days. A significant decrease in the content of gram-negative facultative aerobes in the cecal flora was produced by both allopurinol and azapropazone administration, but these alterations did not correlate with either the incidence of bacterial translocation or the number of enteric organisms present per gram MLN tissue. None of the regimens had any impact on the growth of *Pseudomonas* in the burn wound.

Ileal content of the secondary lipid peroxidation byproduct MDA is shown in Figure 5. Accumulation of MDA in the bowel was significantly reduced by allopurinol treatment on postburn day 1 ($p < 0.05$) and reduced to an even greater extent by fluid resuscitation and azapropazone treatment ($p < 0.01$). However no increase in ileal MDA content occurred in the animals in any of these four burned and infected groups on postburn days 4 and 7, implying an absence of lipid peroxidation activity within the intestine at these times.

Discussion

Failure of the gastrointestinal tract to act as an adequate barrier against the absorption of intraluminal bacteria and toxins as a consequence of systemic stress has been proposed as a potential source of morbidity after thermal injury.[18] Evidence of gut barrier failure has been demonstrated in both animals and humans after cutaneous burns.[1,4–10] Bacterial translocation, the passage of viable enteric bacteria from the intact gastrointestinal tract to the mesenteric lymphatics and beyond,[16] has been widely

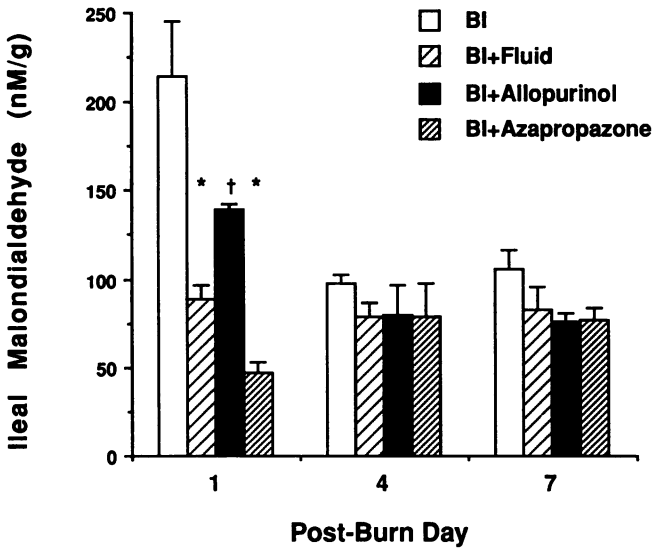

FIG. 5. Ileal malondialdehyde (MDA) content during the 7-day study period. Ileal MDA levels (mean ± SEM) doubled in the BI group on postburn day 1 compared to baseline. This initial increase in lipid peroxidation byproducts was attenuated by fluid (*$p < 0.01$), allopurinol (†$p < 0.05$), and azapropazone (*$p < 0.01$) treatments. Ileal MDA content was not increased in any group on postburn days 4 and 7, despite a high incidence of bacterial translocation.

used as a marker of gut barrier dysfunction in experimental models and has been shown to occur after hemorrhagic shock, endotoxin challenge, and dietary and intestinal flora manipulations, as well as after thermal injury.[1-3,16,19] Gut barrier dysfunction, resulting in bacterial translocation, has been associated with altered regional and systemic responses to subsequent stress[19,20] and may contribute to postinjury hypermetabolism and multiple-organ failure.[21]

Experimental evidence has suggested that gut barrier failure after acute injury may occur as a result of an ischemic insult to the intestine. Intestinal blood flow may be influenced by circulating levels of vasoactive substances such as catecholamines and angiotensin, which are rapidly elevated after thermal injury.[22] Intestinal perfusion then may be further impaired by hypovolemia resulting from fluid sequestration in injured tissues. In animal models, a 50% to 75% increase in splanchnic vascular resistance occurs within 8 hours after a 40% total body surface area full-thickness thermal injury in mini pigs, in association with a 35% decrease in blood flow through the superior mesenteric artery.[23] Reductions in intestinal blood flow of 43% and 46% also have been demonstrated in sheep[6] and rats,[7] respectively, after similar injuries. Maintenance of splanchnic blood flow through pretreatment with an angiotensin-converting enzyme inhibitor[7] or intra-arterial infusion of a vasodilator[8] results in a significantly reduced incidence of bacterial translocation in these models. Furthermore rates of bacterial translocation after thermal injury also may be reduced by pretreatment with xanthine oxidase inhibitors such as allopurinol or tungsten.[9] Thus relative intestinal ischemia appears to be clearly operative in the etiology of bacterial translocation acutely after thermal injury.

Gut barrier dysfunction and bacterial translocation appear to be transient events after thermal injury. In Wistar rats, a 30% scald injury is associated with a 75% incidence of enteric organisms in cultures of the mesenteric lymph nodes on postburn day 1, but the nodes are again sterile by the fourth postburn day.[10] Similarly the number of enteric organisms present in the mesenteric lymph nodes of mice following *E. coli* monoassociation and 30% scald injury decreases 1000-fold between postburn days 1 and 3.[24] These findings imply that repair of the ischemic injury to the gut barrier occurs rapidly after thermal injury.

In contrast the superimposition of a source of infection after thermal injury is associated with prolonged evidence of gut barrier dysfunction. Wistar rats subjected to 30% scald injury and wound inoculation with *Pseudomonas aeruginosa* have similar rates of bacterial translocation on postburn day 1 as animal receiving thermal injury alone, as demonstrated by the BI group in the present study. However infected animals appear to be unable to repair gut barrier damage effectively and clear translocated organisms. Ileal mucosal thickness[10] and synthetic capabilities[11] are severely diminished in burned and infected animals compared to burned or starved animals. A chronic state of gut barrier dysfunction results, leading to an increased incidence of positive mesenteric lymph node cultures by postburn day 4 in infected animals, with a progression of translocated enteric organisms to the abdominal viscera and ultimately into the blood stream not seen after uncomplicated thermal injury.[10]

We sought to determine the role of intestinal ischemia in the etiology of the prolonged gut barrier dysfunction seen in thermal injury complicated by infection. Previously we demonstrated in a model identical to the current BI group that intestinal blood flow, as assessed by ^{51}Cr-labeled microspheres, is maintained at normal levels 3 and 7 days after thermal injury. This finding implies that continued intestinal ischemia is not involved in the etiology of the prolonged gut barrier failure associated with sepsis. However this methodology, while effective at measuring total blood flow to the intestine, does not eliminate the possibility of local ischemia resulting from intramural shunting of blood away from the intestinal mucosa at the villous tips. Thus the three treatment regimens used in the current study were designed to examine further the role of ischemic damage in gut barrier dysfunction during sepsis.

Because fluid sequestration in injured tissues may reduce splanchnic perfusion through intravascular volume depletion and release of vasoconstrictors such as catecholamines and angiotensin, fluid replacement is a logical

measure to prevent intestinal ischemia after injury. A standard replacement formula for animal models was used to calculate the estimated fluid requirement, given by intraperitoneal injection.[13] Adequacy of resuscitation was demonstrated by the maintenance of normal hematocrit values throughout the study period in the BI + Fluid group (Fig. 2), while significant hemoconcentration occurred in the unresuscitated BI group. Accumulation of edema fluid in tissues (Figs. 3 and 4) is similar to that clinically observed in septic burned patients. Tissue damage after ischemic insult results largely from the generation of oxygen free radicals and peroxidases. Allopurinol, through inhibition of xanthine oxidase, reduces oxygen radical formation during ischemia and reperfusion injuries and previously was shown to reduce bacterial translocation after uncomplicated thermal injury.[9] Azapropazone is an anti-inflammatory agent shown to inhibit neutrophil migration, aggregation, and degranulation,[25] and thus reduces both free radical generation as well as direct tissue damage by lipid peroxidation.

The effectiveness of these treatment regimens at reducing the initial intestinal ischemic damage after thermal injury is demonstrated by both the reduced rate of bacterial translocation (Table 1) and the prevention of accumulation of lipid peroxidation byproducts in intestinal tissues (Fig. 5) on the first postburn day. However neither fluid resuscitation nor inhibition of xanthine oxidase or neutrophil degranulation had any impact on the prolonged gut barrier failure associated with the onset of sepsis, as evidenced by the high rates of bacterial translocation on postburn days 4 and 7. The systemic progression of translocating organisms probably reflects alterations in host defenses attendant with the development of sepsis. Ileal MDA content, after an initial increase on postburn day 1 in the untreated BI group, returned to baseline levels in this group on postburn days 4 and 7. No significant elevations in ileal MDA were noted in the treatment groups on postburn days 4 and 7 despite a high incidence of bacterial translocation. Therefore these data indicate that the prolonged gut barrier failure associated with sepsis after acute injury in this model appears to occur independently of continued intestinal ischemic damage. Failure to eliminate translocated bacteria due to host immunosuppression, as suggested by Penn et al.,[26] also may contribute to the prolonged presence of enteric organisms in the MLN and to the systemic progression of translocated bacteria.

Acute thermal injury results in a constellation of systemic host responses that produce effects on body tissues far removed from the area of injury. Host responses such as the production and release of inflammatory and vasoactive mediators occur transiently after simple injury and may contribute to regional alterations in perfusion, relative intestinal ischemia, and the development of gut barrier failure with bacterial translocation. In the absence of complications after acute injury, damage to the gut barrier is quickly repaired and translocated organisms are cleared (Fig. 6). However acute responses to injury may be sustained and exaggerated by the subsequent superimposition of a focus of infection, such as may occur during burn wound sepsis, interfering with repair processes and leading to further gut barrier dysfunction with continued bacterial translocation.

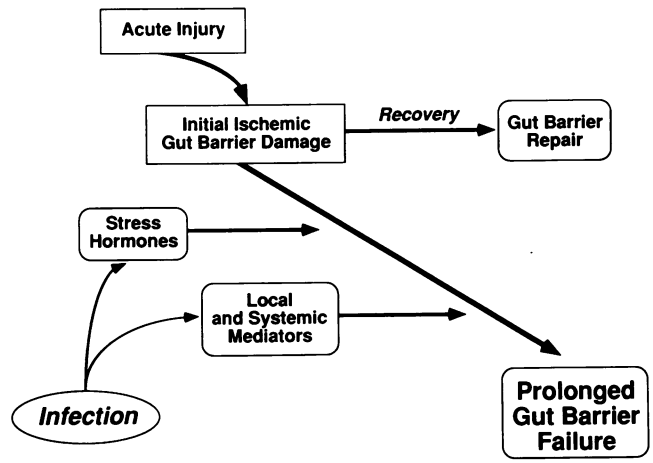

FIG. 6. Proposed pathophysiology of gut barrier failure after acute injury, and injury complicated by subsequent infection.

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